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A common and functional mineralocorticoid receptor haplotype enhances optimism and protects against depression in females

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Mineralocorticoid (MR) and glucocorticoid receptors (GR) are abundantly expressed in the limbic brain and mediate cortisol effects on the stress-response and behavioral adaptation. Dysregulation of the stress response impairs adaptation and is a risk factor for depression, which is twice as abundant in women than in men. Because of the importance of MR for appraisal processes underlying the initial phase of the stress response we investigated whether specific *MR* haplotypes were associated with personality traits that predict the risk of depression. We discovered a common gene variant (haplotype 2, frequency ~0.38) resulting in enhanced MR activity. Haplotype 2 was associated with heightened dispositional optimism in study 1 and with less hopelessness and rumination in study 2. Using data from a large genome-wide association study we then established that haplotype 2 was associated with a lower risk of depression. Interestingly, all effects were restricted to women. We propose that common functional *MR* haplotypes are important determinants of inter-individual variability in resilience to depression in women by differentially mediating cortisol effects on the stress system.
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Introduction

A fundamental question in mental health research is why some individuals can cope with stress while others can't and become vulnerable for depression. Tipping the balance from resilience to vulnerability occurs upon dysregulation of brain mineralo- (MR)- and glucocorticoid receptors (GR), which mediate the action of the adrenal hormone cortisol on the initiation and termination of the stress response, respectively.[1,2] Chronically elevated cortisol activating GR is a known risk factor for depression[3] and blockade of excess cortisol with GR antagonists has been successful in the treatment of psychotic depression.[4] In addition, abundant evidence points to MR activation in the limbic brain as a potential antidepressant strategy.[3,5–9]

Previously we identified two single-nucleotide polymorphisms (SNPs) located in exon 2 of the *MR* (*NR3C2*) gene (−2G/C and I180V; Figure 1a) that influence MR translation and/or its capacity to transactivate target genes in cell lines. These two SNPs caused differential neuroendocrine and sympathetic responses to psychological stressors.[10,11] In addition, these SNPs were associated with differences in the cortisol awakening response, depending on an interaction with selective serotonin reuptake inhibitors or after dexamethasone treatment.[12,13] Most of the associations found with the *MR* SNPs were sex-dependent. Here, we assessed whether the functional SNPs in exon 2 are linked to SNPs in the *MR* promoter region, which potentially influence *MR* transcription and its dynamic expression. We identified a common gene variant (haplotype 2, frequency ~0.38) that enhances MR synthesis. Next, our objective was to examine if the *MR* haplotypes protect against depression. We discovered that *MR* haplotype 2 enhances resilience to depression, particularly in women and have replicated this finding in three independent studies, including data from a genome-wide association study.

Materials and methods

SNP analysis of the *MR* promoter region and luciferase assays. A total of 50 anonymous blood samples were obtained from the general physician laboratory in Leiden. DNA was isolated and the *MR* gene's coding sequence was analyzed for the occurrence of SNPs, including the −2G/C and I180 V SNPs, as described by DeRijk *et al.*[14] In the present study, a region of almost 4 kb (3870 basepairs) of the 5′ untranslated region (5′ UTR) was amplified with multiple PCR reactions followed by sequence analysis. Based on the literature and with *in silico* analysis we verified whether the

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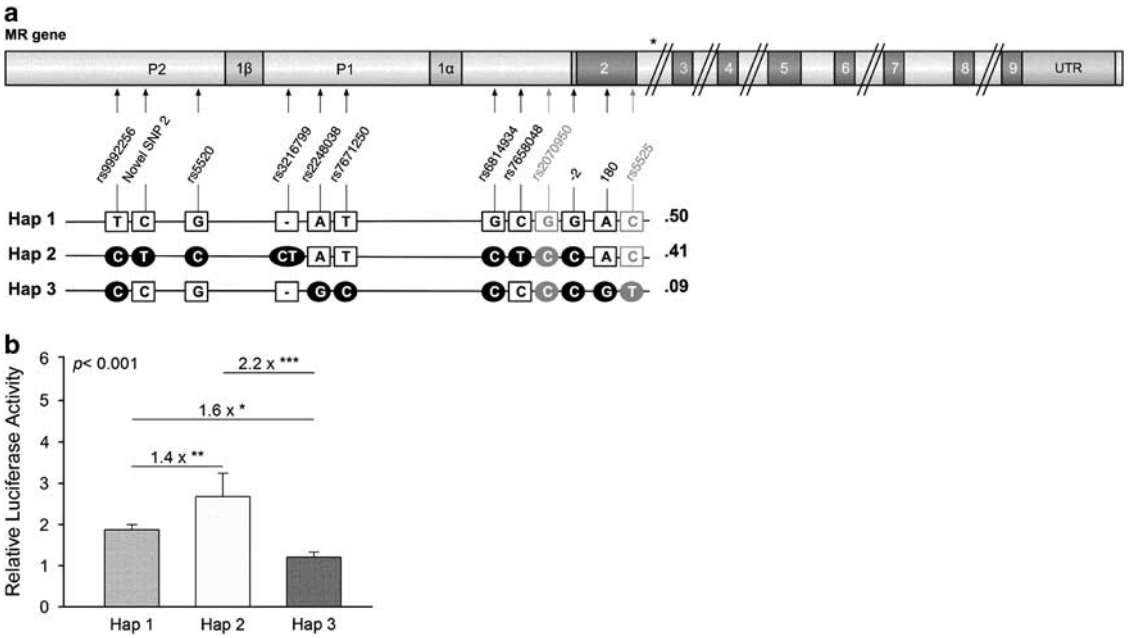

Figure 1 (**a**) Schematic overview of the human mineralocorticoid receptor (*MR)* gene with its respective 5′ haplotypes and haplotype frequencies. Three haplotypes along a stretch of 4 kb of the 5′ untranslated region were identified based on the genotypes of 50 anonymous DNA samples and include eight single-nucleotide polymorphisms (SNPs). The positioning and relation with the -2G/C (rs2070951) and I180 V (rs5522, control SNPs in grey) SNPs are indicated, which tag these three most common haplotypes. The haplotypes are not linked to common SNPs more 3′ in the *MR* gene sequence, as a recombination hotspot exists in intron 2 (asterisk). (**b**) Mean activity (± s.e.m., $N = 6$) of the human *MR* promoter region associated with haplotype 1, 2 or 3. The figure shows representative results (of three independent experiments with two distinct sets of plasmid isolates) on the comparison of promoter activities associated with haplotype 1–3 relative to the activity of the pGL3-Basic plasmid, which activity was set to 1 (data not shown). Activities differed significantly between the three MR plasmids ($F(2,15) = 27.98$; $P < 0.001$). Data are firefly luminescent signals divided by the *Renilla* luminescent signals, hereby controlling for cell death and variability in transfection efficiency. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. Abbreviations: P1, promoter 1; P2, promoter 2; UTR, untranslated region.

common SNPs in this 4 kb promoter region were located in (predicted) transcription factor- (TF) binding sites, glucocorticoid responsive elements, binding of other steroid receptors (using the TF databases TRANSFAC[15] and JASPAR[16]), or whether they would influence splicing of the MR transcripts.[17]

Haplotypes were reconstructed and for the three haplotypes with a frequency above 0.03 (designated as haplotype 1, 2 or 3) firefly luciferase reporter plasmids were constructed using the pGL3-Basic plasmid (Promega, Leiden, The Netherlands). Two separate bacterial cultures and plasmid DNA isolates were prepared for each of the three haplotype-firefly luciferase constructs on two distinct days. Differential promoter activity between the three haplotypes was tested in human neuroblastoma cells (BE(2)-M17; Health Protection Agency Culture Collections, Cat. No. 95011816). Cells were transfected with 200 ng of haplotype-firefly luciferase construct 1, 2 or 3, together with 10 ng of a *Renilla* luciferase reporter plasmid (pGL4.74 (*hRluc*/TK), Promega). In separate culture wells, 100 ng of pGL3-Basic or pGL3-Control vector (Promega) were transfected, functioning as, respectively, background measurement or positive control. Each construct was transfected in six separate wells. After 48 h of incubation, cells were lysed and firefly and *Renilla* luminescent activity was assessed. Experiments were performed three times on separate days for each of the two sets of plasmid DNA isolates. Relative light units were calculated by dividing the firefly luminescent signals by the corresponding *Renilla* luminescent signals in order to correct for variability in transfection efficiency or cell death (see Supplementary Methods and Supplementary Table 1 for further details).

Study 1: association with dispositional optimism. The first study group consisted of 450 elderly men and women who previously participated in the 9.1-year longitudinal Arnhem Elderly Study[18] (see Supplementary Methods and Supplementary Table 4 for sample characteristics). Dispositional optimism was assessed using the Dutch Scale of Subjective Well-being for Older Persons (Groningen University, The Netherlands).[19] The Dutch Scale of Subjective Well-being for Older Persons consists of five subscales including *Health*, *Self-respect*, *Morale*, *Contacts* and *Optimism*. For each subscale an individual could indicate to what extent it conforms to a particular statement on a 3-point scale (from 0 to 2). An example of one of the seven statements for optimism is: 'I still have positive expectations concerning my future' (our translation). A mean item score for the optimism subscale was calculated and multiplied by 10, resulting in scores ranging from 0 to 20, with higher scores indicating a higher level of optimism. Participants provided a blood sample for genotype analysis. This study was approved by the Medical Ethics Committee of Wageningen University (Wageningen, The Netherlands). All participants provided written informed consent.

Study 2: association with cognitive reactivity to sad mood. As a follow-up on the first study, this second study was performed to test the association between the *MR* haplotypes and hopelessness, which is by definition inversely related to optimism. The second study group consisted of 150 university students (see Supplementary Methods and Supplementary Table 5 for sample characteristics). Thoughts of hopelessness during sad mood as well as several other measures of cognitive reactivity were assessed with the Leiden Index of Depression Sensitivity-revised.[20] It is a self-rating questionnaire consisting of 34 items and six subscales, namely *Hopelessness/Suicidality*, *Acceptance/Coping*, *Aggression*, *Perfectionism/Control*, *Risk Aversion* and *Rumination*. An example of one of the five statements for *Hopelessness/Suicidality* is: 'When I feel down, I more often feel hopeless about everything'. Participants had to indicate whether and how their thinking patterns change when they experience mild dysphoria, by scoring each item on a 5-point Likert-scale ranging from 0 'not at all' to 4 'very strongly'. Scores for *Hopelessness/Suicidality* range from 0 to 20.

In addition, scores were assessed for neuroticism (Neuroticism-Extraversion-Openness Five-Factor Inventory[21]), current symptoms of anxiety and depression (Hospital Anxiety and Depression Scale[22]) and the presence of current and past depression (Major Depression Questionnaire[23]). Participants provided a saliva sample for genotype analysis. This study was approved by the Ethics Committee of the Leiden University Medical Center (Leiden, The Netherlands). All participants gave written informed consent.

Study 3: association with the risk of depression. To test association of the *MR* haplotypes with major depressive disorder (MDD) in a larger study sample, data were used from a genome-wide association study, the GAIN-MDD study.[24] MDD cases ($n=1730$) were mainly from the Netherlands Study of Depression and Anxiety (NESDA; http://www.nesda.nl).[25] The patients included here had a lifetime diagnosis of MDD as diagnosed with the *DSM-IV* Composite International Diagnostic Interview version 2.1.[26] The control subjects ($n=1793$; mean age $\pm$ s.d. $= 45.1 \pm 14.1$), having no report of MDD, were mainly from the Netherlands Twin Registry (http://www.tweelingenregister.org).[27] Participants provided a blood sample for genotype analysis. The NESDA and The Netherlands Twin Registry studies were approved by the Central Ethics Committee on Research Involving Human Subjects of the VU University Medical Center, Amsterdam, The Netherlands. All subjects provided written informed consent (see Supplementary Methods and Supplementary Table 6 for sample characteristics).

DNA isolation and genotyping. DNA was isolated from the blood (first and third study group) or saliva (second study group) samples and genotypes were assessed for the functional *MR* −2G/C (rs2070951_GC) and I180V (rs5522_AG) SNPs, which tag the three most common haplotypes localized in exon 2 and extending into the promoter region (Figure 1a; see Supplementary Methods and Sullivan *et al.*[24] for further details).

Statistical analysis. SNP allele frequencies were tested for Hardy–Weinberg Equilibrium using HaploView (version 4.1. for Mac OS X; available online, http://www.broadinstitute.org/mpg/haploview).[28] In addition, HaploView was used to assess inter-marker linkage disequilibrium (LD) scores (expressed as *D'* and r^2) between the *MR* SNPs and to reconstruct haplotypes. Individual haplotypes were reconstructed in SNPHAP (version 1.3; available online, http://www-gene.cimr.cam.ac.uk/clayton/software/snphap.txt).

To compare promoter activities between the three constructs containing haplotype 1, 2 or 3, a one-way analysis of variance was conducted followed by a *post hoc* Bonferroni multiple comparison test.

Differences between men and women on the various demographics and health factors were tested using an independent-samples *t*-test, a χ^2-test or a Mann–Whitney *U*-test, where appropriate. A square-root transformation was performed for the *Hopelessness/Suicidality*, *Acceptance/Coping*, *Aggression*, *Perfectionism/Control*, Hospital Anxiety and Depression Scale-depression and -total scales and for age of the student participants of study 2 (when comparing age between men and women) in order to normalize their distributions. Figures 2, 3a and b and Supplementary Tables 4–6 represent untransformed data, while statistical tests were performed on transformed data where appropriate (indicated with an asterisk). Supplementary Table 7 represents transformed data and statistical analysis where appropriate.

For association analysis with the haplotypes, three dummy variables were created indicating whether a person carried zero, one or two alleles of haplotype 1, 2 or 3. With linear regression analysis the mean effect of one haplotype 2- or 3-allele on a psychological trait was determined relative to the reference group (scores in haplotype 1 carriers). To determine the effect of two haplotype 2- or 3-alleles, the effect calculated for one allele can be multiplied by 2. Because of possible sex

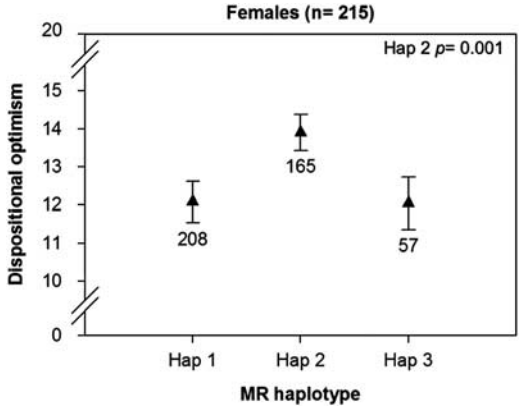

Figure 2 Results of study 1, showing crude mean scores ($\pm$ s.e.m.) for dispositional optimism according to three 5′ mineralocorticoid receptor (*MR)* haplotypes in women. Dispositional optimism scores increased 1.7 per haplotype 2 allele (on a range of 0 to 20) only in women (explained variance = 7%) and not in men (Supplementary Table 7). To determine the effect of two haplotype 2- or 3-alleles, the effect calculated for one allele can be multiplied by 2. *P*-values represent adjusted comparison of haplotype 2 to the reference (haplotype 1 carriers) with linear regression. Note the breaks in the *y* axis.

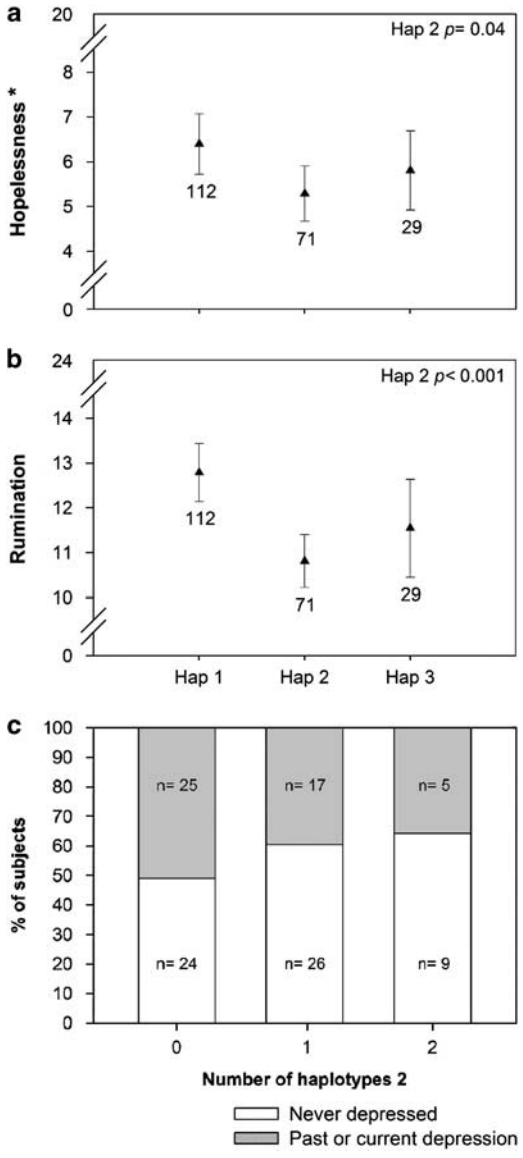

Figure 3 (**a**, **b**) Results of study 2, showing crude mean scores (± s.e.m.) for cognitive reactivity according to three 5′ *MR* haplotypes in women. Hopelessness (**a**) scores decreased 1.1-fold per haplotype 2 allele (on a range of 0 to 20), only in women (explained variance = 4%) but not in men (Supplementary Table 7). In addition, rumination (**b**) scores were lower only in the female haplotype 2 carriers, with a 2.1-fold reduction per haplotype 2 allele (on a range of 0 to 24; explained variance = 11%). To determine the effect of two haplotype 2- or 3-alleles, the effect calculated for one allele can be multiplied by 2. *P*-values represent adjusted comparison of haplotype 2 to the reference (haplotype 1 carriers) with linear regression. Note the breaks in the *y* axis. * Statistical test based on transformed data. (**c**) Percentage of female students reporting a diagnosis for depression according to the number of haplotypes 2 (odds ratio = 0.40; 95% confidence interval = 0.16–0.95; $P = 0.04$). For statistical test results see also Supplementary Table 8a.

differences, statistical interaction between the *MR* haplotypes and sex was determined by adding the two appropriate interaction terms to the model. Next, regression analyses were repeated in sex strata. In sensitivity analyses in study 2 subjects without a European ancestry were excluded. In study 2 associations between the haplotypes with the other Leiden Index of Depression Sensitivity-revised subscales, neuroticism and current symptoms of anxiety and depression was also tested. Logistic regression was used to test association with self-reported diagnosis of depression. In the third association study, logistic regression was used to test association with MDD. As sex-dependent associations are potentially due to differences in circulating sex steroids, the group of women of the GAIN-MDD study was additionally divided in women older and younger than the mean age for menopause (~51 years). In all three studies, analysis was repeated while adjusting for potential confounding effects of sex (in the total group) and age.

A two-sided *P*-value <0.05 was considered statistically significant. A Bonferroni correction was applied where appropriate. All statistical analysis was performed in SPSS, version 16.0 for Mac OSX (SPSS, Chicago, IL, USA).

Results

***MR* SNP and haplotype frequencies and predicted effects on *MR* transcription.** In all, 16 SNPs were detected along the 4 kb *MR* promoter region. As of October 2011, three SNPs were still not reported elsewhere (GRCh37:4:149362585:149366454, Ensembl; novel SNP 1, 2 and 3). All allele frequencies of the *MR* SNPs were in Hardy–Weinberg Equilibrium ($P>0.10$; see Supplementary Table 2 and Supplementary Figure 1 for an overview of individual SNP genotype frequencies and inter-marker r^2 scores). Reconstruction of *MR* haplotypes resulted in one haplotype bin that was highly linked to the previously described *MR* -2G/C and I180V SNPs. On the basis of previous research by our lab and the HapMap database (http://hapmap.ncbi.nlm.nih.gov) we know that these exon 2 SNPs are not linked to the rest of the *MR* gene sequence starting in intron 2.[14]

Pooling the low frequency haplotypes (freq. <0.03) with the high frequency haplotypes (based on the −2G/C and I180V genotypes) resulted in three haplotypes with frequencies of 0.50, 0.41 and 0.09, which differ in eight *MR* 5′ UTR SNPs (Figure 1a). These eight *MR* 5′ UTR SNPs were not located at previously described TF-binding sites. However, *in silico* analysis using two different databases consistently predicted the SNP rs5520 to affect the number of possibilities for Sp1 binding, while the SNP rs3216799 influences Hepatocyte Nuclear Factor 1 b binding (see Supplementary Table 3). Of interest is that one database predicted the SNP 2248038 to affect a glucocorticoid responsive element-consensus sequence by influencing binding of NR3C1 (or GR), while the SNP rs3216799 was predicted to be located 1 nucleotide next to a glucocorticoid responsive element (data not shown). The SNPs did not alter predicted splicing of the MR transcripts.

Promoter haplotype 2 results in higher MR expression. Results of three independent experiments with two separate sets of plasmid isolates were highly similar. All three *MR* promoter regions were active under non-stimulating conditions, as the constructs resulted in a signal that was higher compared with the pGL3-Basic

plasmid (Figure 1b). Activities between the three plasmids differed significantly ($F(2,15) = 27.98$; $P < 0.001$). Haplotype 2 resulted in a 1.4 times higher promoter activity compared with haplotype 1 ($P < 0.01$) and a 2.2 times higher promoter activity compared with haplotype 3 ($P < 0.001$).

Haplotype frequencies in the three association study groups. Allele frequencies of the *MR* SNPs were in Hardy–Weinberg Equilibrium ($P > 0.10$). Genotype and haplotype frequencies (see Supplementary Tables 4–6) and inter-marker correlations between the *MR* -2G/C (rs2070951) and I180V (rs5522) SNPs ($D' = 1.0$; $r^2 = 0.15$) were similar as previously found.[10]

Study 1: *MR* haplotype 2 associates with higher dispositional optimism, specifically in women. *MR* haplotype 2 (freq. 0.36) was associated with higher dispositional optimism when compared with the reference group (haplotype 1 carriers; $P = 0.01$; Supplementary Table 7). Importantly, a *MR* haplotype 2-by-sex interaction effect was found ($P = 0.01$). Data stratification for sex revealed that only in women haplotype 2 was related to higher levels of dispositional optimism (Figure 2) with an explained variance was 7% ($R^2change = 0.07$), while no significant effect was found in men.

Study 2: *MR* haplotype 2 associates with fewer thoughts of hopelessness, specifically in women. Haplotype 2 was significantly associated with fewer thoughts of hopelessness, again only among female students (Figure 3a), with an explained variance of 4% ($R^2change = 0.04$).

Interestingly, additional analysis of the other five Leiden Index of Depression Sensitivity-revised subscales showed that in women haplotype 2 was also significantly associated with lower scores for aggression ($P = 0.007$), risk aversion ($P = 0.05$) and importantly, rumination (Figure 3b; $P < 0.001$; after a Bonferroni correction for in total twelve tests for the association with six subscales in both sexes, with a significance threshold of $P < 0.004$, this is still significant). Moreover, in women *MR* haplotype 2 associated with lower neuroticism scores ($P = 0.04$), a lower odds ratio for self-reported diagnosis of depression according to a dominant model (0.40; 95% confidence interval = 0.16–0.95; $P = 0.04$; Figure 3c and Supplementary Table 8a; similar results were found with a linear model but showed smaller effect sizes) and a trend was found for less symptoms of depression ($P = 0.07$, see Supplementary Results and Supplementary Table 7).

Results strengthened after excluding subjects (22 women, 4 men) who indicated that one or both of their parents did not have a European ancestry or who did not respond to this question.

Study 3: *MR* haplotype 2 associates with a lower risk of major depressive disorder, specifically in women. The data of study group 3 were analyzed in two steps and revealed that *MR* haplotype 2 was associated with a lower risk of depression again only in women and not in men, but strongly depending on whether the women were aged above or below the mean age for menopause (~51 years). In the first step a trend was found for an association between *MR* haplotype 2 and a lower odds ratio for MDD in the total group of women (0.85; 95% confidence interval = 0.72–1.02; $P = 0.08$) and not in men ($P = 0.72$), again according to a dominant model (Figure 4a and Supplementary Table 8b; similar results were found with a linear model but showed smaller effect sizes). Importantly, data stratification for the mean age for menopause in the second analysis step (*MR* haplotype 2-by-age split at 51 years interaction $P = 0.004$) showed that *MR* haplotype 2 associated with a

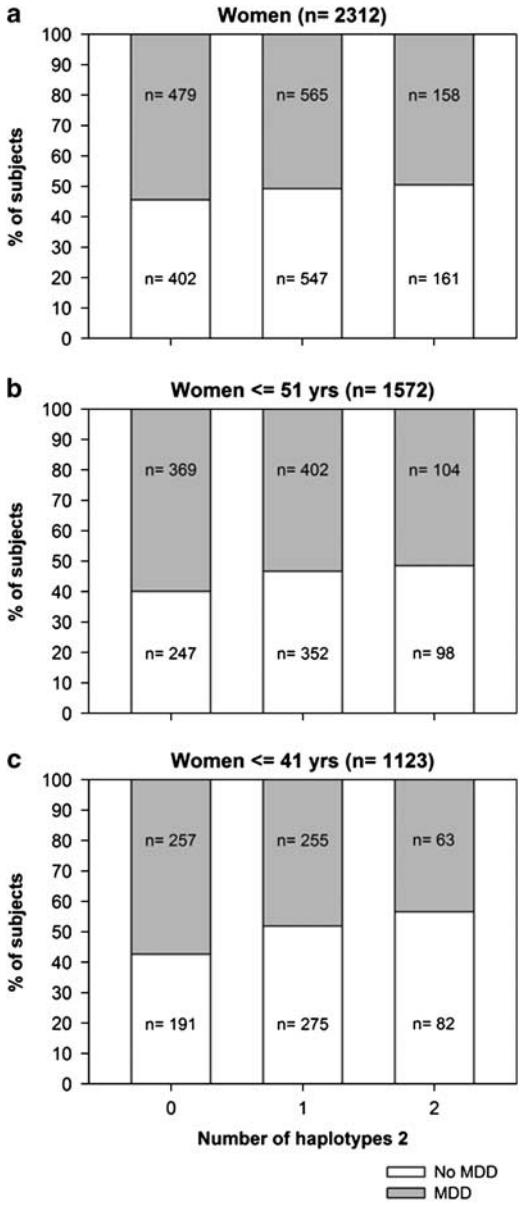

Figure 4 Results of study 3, showing the percentage of women diagnosed with major depressive disorder (MDD) according to the number of haplotypes 2. Results are presented for the total group of women (**a**) (odds ratio = 0.85; 95% confidence interval = 0.72–1.02; $P = 0.08$), for the women aged ⩽51 years (odds ratio = 0.75; 95% confidence interval = 0.60–0.93; $P = 0.009$) (**b**), or for the women aged ⩽41 years (odds ratio = 0.66; 95% confidence interval = 0.52–0.86; $P = 0.002$) (**c**). MDD cases were mainly from the Netherlands Study of Depression and Anxiety cohort (NESDA),[25] healthy controls were mainly from the Netherlands Twin Registry (NTR).[27] For statistical test results see Supplementary Table 8b.

lower odds ratio for MDD specifically in the women with an age $\leqslant$51 years (0.75; 95% confidence interval = 0.60–0.93; $P = 0.009$; after a Bonferroni correction for in total four tests for association analysis within both sexes and within the two age groups, with a significance threshold of $P < 0.0125$, this is still significant; Figure 4b). The association particularly existed in the women with an age $\leqslant$41 years (0.66; 95% confidence interval = 0.52–0.86; $P = 0.002$; Figure 4c; *MR* haplotype 2-by-age split at 41 years interaction $P = 0.008$).

Discussion

The findings show that in three distinct groups of subjects the common and functional *MR* haplotype 2 was associated with optimism and a lower risk of depression in women. Haplotype 2, consisting of the known −2G/C and I180V SNPs[11,13,29] and several promoter SNPs results in higher MR activity at the transcriptional, translational and transactivational level.[10] Previously, MR expression was found to be decreased in the limbic brain of depressed subjects.[6] Moreover, the MR is induced by antidepressant treatment, with MR induction potentially contributing to antidepressant treatment success.[8,9] MR agonists and antagonists either enhance or suppress antidepressant efficacy, respectively,[5,7] whereas modulatory effects of SNPs in the *MR* gene on the cortisol response to stress have been reported.[10,11] This implicates cortisol action via the MR as an important determinant of the inter-individual differences in stress responsiveness and vulnerability for depression. Indeed, in a previous study an association was found between the *MR* I180V SNP and geriatric depression.[29]

Possibly the *MR* promoter SNPs are to a large extent responsible for the inter-individual differences. MR expression is highly dynamic, showing changes during development, aging and after physical or psychological stress.[30–35] Context-dependent changes in MR expression can be established by distinct 5′ *MR* mRNA transcripts (MRα and MRβ), each having its own promoter containing regulatory elements and showing differential expression depending on tissue, time and availability of steroids and stress.[6,30,36–38] SNPs may result in differential expression of MRα vs MRβ by affecting TF binding or splicing. Two of the eight common 5′ UTR SNPs were consistently predicted to influence TF binding while a third SNP was predicted to affect a glucocorticoid responsive element-consensus sequence (although not consistent). None of the SNPs was predicted to affect potential binding sites for sex steroids. Additional *in vitro* assays, like electrophoretic mobility shift assays, are necessary to identify allele-specific TF binding.

Intriguingly, the *MR* haplotype 2 appears to establish a lower risk of depression diagnosis only in women below 51 and in particular below 41 years of age. This suggests that female sex steroids may interact with the *MR* gene, thereby modulating resilience. The *MR* haplotypes are known to confer differences in MR activity with varying ligand availability, while hypothalamic-pituitary-adrenal (HPA) responses to stress are sex-specific.[10,39] Moreover, estrogens and progesterone are known to modulate MR mRNA and/or protein expression, with possible consequences for stress-reactivity.[40,41] These effects of sex steroids are superimposed on the remarkable promiscuity of the brain MR, which can bind also aldosterone and progesterone, but is particularly occupied by the much higher concentrations of circulating cortisol. This is because the cortisol-inactivating enzyme typical for aldosterone selectivity of the MR in kidney epithelial cells is absent in brain.[42] However, no significant interaction effect was found between the haplotypes and the use of oral contraceptives (data not shown). Furthermore, the age difference in the association between the *MR* haplotypes and depression diagnosis may also be because of the impact of genetic factors, which is known to be larger for early-onset rather than late-onset depression.[43] Although study group 1 and particularly study group 2 were small, with a rather low power to detect haplotype-related differences, the three independent studies, including the larger genome-wide association study dataset, all pointed to similar and significant associations.

In the limbic brain higher MR activity implies an enhanced reaction to novel information, allowing the individual to better appraise and perceive a new experience as either stressful or not. Individuals at risk of depression are thought to cope less efficiently with challenges,[44] a phenomenon clearly linked to cortisol resistance in the brain to which haplotypes 1 and 3 with reduced activity of the *MR* may contribute. Also, hopelessness and rumination associated with these haplotypes are risk factors for depression; rumination is a strong predictor of depressive episodes (correlation = 0.42 for previous Beck Depression Inventory (BDI) depression, 0.55 for current BDI depression), whereas hopelessness is not only a predictor of depressive episodes (correlation = 0.57 for previous BDI depression, 0.40 for current BDI depression), it is also related to suicidal ideation during and between depressive episodes.[45–47] In contrast, the dispositional optimism associated with haplotype 2 is a rather stable trait that relates to successful coping with stressful experiences and predicts a lower risk of depression (Spearman's correlation coefficient = −0.50 to −0.63 for depressive symptoms among elderly during 15 years of follow-up).[48,49]

Our data strengthen the hypothesis that disturbed cortisol effects through impaired central MR signaling underlie in part the pathophysiology of depression.[1,3] The MR mediates cortisol-enhanced metaplasticity in the limbic brain involving the recently discovered membrane variants[50] and the cortisol effects on appraisal, cognitive and behavioral flexibility and emotions.[29,51–54] As the hormone cortisol drives gene-environment interaction, for better, but also for worse, the data raise the possibility that the cortisol-MR complex functions similarly as the recently designated 'plasticity genes' (like the serotonin transporter gene with its well-known 5-HTTLPR polymorphism), with the reactive alleles rendering an individual more susceptible to adverse conditions, but also providing a benefit under supportive conditions.[55]

Here, we show that men's susceptibility to depression does not seem to be modulated by *MR* gene variability, while women's susceptibility depends on whether they carry *MR* haplotype 1 or 3 vs haplotype 2. That the *MR* haplotype 2 enhances psychological resilience particularly in women is fascinating considering the twice higher prevalence of depression in women.[56] The finding provides a new lead towards a better understanding of the pathogenesis of this devastating affective disorder.

Conflict of interest

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Translational Psychiatry website (http://www.nature.com/tp)